Case Report

Mucinous cystadenoma of the ovary with functioning stroma and virilization in pregnancy: A case report and review of the literature

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Summary

Virilization caused by ovarian tumors with functioning stroma during pregnancy is extremely rare and has been reported in many ovarian tumors. In mucinous cystadenomas with maternal virilization during pregnancy the stromal cells responsible for the hormone secretion resemble lutein or Leydig cells and have been referred to as luteinized stromal cells. We present a case of a 30-year-old, gravida 2, para 1, woman who presented at approximately the 38th week of pregnancy with features of virilization. At the same time, a cesarean section was performed because of fetal distress and a male weighing 3,030 g without any gross abnormalities was delivered. A large tumor of the right ovary was detected and a right salpingo-oophorectomy was performed. Histopathologically, the tumor proved to be a benign mucinous cystadenoma. Masses typically resembling lutein stromal cells or Leydig cells of the testes or ovarian hilus were found in the wall of the cyst below the mucinous epithelium. No crystalloids of Reinke were identified. The stromal component of the tumor was characterized as functioning stroma with luteinized stromal cells. The glandular mucinous epithelium showed focal positivity for human chorionic gonadotrophin. The cytoplasm of the luteinized stromal cells reacted strongly and diffusely with antiserum for vimentin. Also, the cytoplasm of the luteinized stromal cells showed focal intense positivity for synaptophysin, and focal mild positivity for human chorionic gonadotrophin. Staining results for oestrogen and progesterone receptors were negative. In conclusion, we present an unusual case of clinical virilization during pregnancy associated with an ovarian mucinous cystadenoma with functioning stroma. The virilizing manifestations disappeared after removal of the ovarian neoplasm, supporting the perception that the functioning ovarian stroma was responsible for the androgen production.

Key words: Virilization; Pregnancy; Leydig cell hyperplasia; Functioning ovarian stroma; Luteinization; Hilar cell hyperplasia; Mucinous ovarian cystadenoma.

Introduction

Androgen-secreting ovarian neoplasms are rare [1] and include: (i) sex cord-stromal tumours (granulosa cell tumors, thecomas, sclerosing stromal tumours and Sertoli-Leydig cell tumours) [1, 2]; (ii) lipid or steroid cell tumours, which are composed entirely of steroid-secreting cells (lutein cells, Leydig cells, and adrenal cortical cells) [1, 3] and (iii) ovarian tumours with functioning stroma [4].

Ovarian tumours with functioning stroma can be divided into three groups: (a) germ cell tumours containing syncytiotrophoblast cells, (b) tumours with functioning stroma occurring during pregnancy and (c) the idiopathic group. Germ cell tumours such as dysgerminomas with synciotrophoblast giant cells, choriocarcinomas, embryonal carcinomas, polyembryomas and mixed primitive germ cell tumours may cause manifestations of steroid hormone secretion as a result of hCG stimulation of the ovary contralateral to the tumour to form luteinized follicles that secrete steroid hormones [4, 5]. Virilization caused by ovarian tumours with functioning stroma during pregnancy is extremely rare [6] and has been reported in many ovarian tumours, such as mucinous cystadenomas or cystadenocarcinomas, Brenner tumours, Krukenberg tumours, benign cystic teratomas and dysgerminomas [1, 7]. In mucinous cystadenomas with maternal virilization during pregancy the stromal cells responsible for hormone secretion resemble lutein or Leydig cells and have been referred as luteinized stromal cells [4, 8, 9]. Patients with primary or metastatic ovarian tumours with functioning stroma in the idiopathic group are usually postmenopausal [4] and the steroid cells are either lutein cells within adjacent ovarian stroma, Leydig cells within the ovarian stroma or hilus cells along the hilar border of the tumour [4].

The produced excessive quantities of androgens by ovarian neoplasms in pregnancy are aromatised to oestrogen by the placenta [1]. However, in some cases female fetuses are not protected by this capacity of the placenta to aromatize large guantities of androgens to oestrogens and are virilized; the clinical hallmark is ambiguous external genitalia [10].

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The purpose of this study was to present an extremely rare case of virilization during pregnancy due to a primary mucinous cystadenoma, with functioning stroma. Also, the relevant international literature is reviewed.

Case Report

A 30-year-old, gravida 2, para 1, woman presented at approximately the 38th week of pregnancy with features of virilization. The patient had no other endocrine symptoms and her past medical history was otherwise unremarkable. Pubertal events were confined to normal patterns with menarche at age 14. Menstrual cycles were regular, every 27 to 35 days and lasted for seven days. There was no history of induced or spontaneous abortion. During pregnancy she felt well and did not seek medical care. She reported noting acne and onset of facial hair at the seventh week of gestation. Physical examination at admission revealed acne on the face and upper trunk, hair on the chin, extremities, chest and abdomen and enlargement of the clitoris. The ovaries could not be visualized by ultrasonography. The androgens serum levels were not determined prior to surgery.

A cesarean section was performed because of fetal distress and a male weighing 3,030 g without any gross abnormalities was delivered. A large tumour of the right ovary was detected. The left ovary was unremarkable. A right salpingo-oophorectomy was performed. A preliminary diagnosis of benign mucinous cystadenoma was made on the basis of frozen-section histology. The postpartum course was uncomplicated and the mother and baby were discharged on the seventh day postpartum. No endocrine disorders were found in the neonate. The patient has been followed up regularly. The acne on the face and upper trunk cleared up one month after the operation. Hair growth on the chin, legs and abdomen returned to normal after two months and there was a marked reduction in the size of the clitoris. The patient experienced a normal menstrual period eight weeks postpartum. The androgen serum levels were normal two months after the operation. The patient was able to nurse the infant for eight months.

Pathology

Material and Methods

The surgical specimen was fixed in 10% formalin. Representative samples were embedded in paraffin and 4 μm thick sections were stained with haematoxylin and eosin. Immunohistochemical analysis was performed using an indirect immunoperoxidase techique with dianobenzidine (DAB) as a chromogen. The following primary antibodies were used: β-human chorionic gonadotrophin (polyclonal antibody, 1:250 dilution, Daco, Denmark), oestrogen receptors (clone 1d5, prediluted, Immunon, Pittsburgh), progesterone receptors (clone 1Aβ, prediluted, Immunon, Pittsburgh), vimentin (clone V9, 1:10 dilution, Daco, Denmark) and synaptophysin (clone SYPO2, prediluted, Neomarkers).

Results

Gross findings

The surgical specimen was found to consist of a 9 cm long and normal fallopian tube and a large tumor measuring 13 x 10 x 7 cm that had completely replaced the ovary and exhibited a smooth external surface with an intact capsule. The cut surface showed a unilocular cystic lesion containing mucinous fluid. The cyst wall was thin, measuring 0.8 cm in the maximum diameter and with diaphragms in some areas of its internal surface.

Microscopic findings

Histologically the tumor proved to be a benign mucinous cystadenoma. The cystic formation was lined by tall columnar, mucous secreting, nonciliated cells. The epithelium was of endocervical (mainly) and intestinal type. No areas of architectural complexity, nuclear stratification or cellular atypia were observed.

Masses typically resembling lutein stromal cells or Leydig cells of the testes and ovarian hilum were found in the wall of the cyst below the mucinous epithelium (Figures 1, 2, 3). These areas showed a solid pattern consisting of epithelial-like polygonal cells with large prominent spherical nuclei and bulky pink cytoplasm arranged in sheets, but no formation of acini or ducts was noted (Figure 1). These cells showed a distinct cell border with eosinophilic cytoplasm. Their nuclei showed no pleomorphism (Figure 4). No mitotic figures were detected. Small nucleoli were observed. No crystalloids of Reinke were identified, nor did they contain mucin. The stromal component of the tumour was characterized as functioning stroma with luteinized stromal cells. The adjacent fallopian tube was unremarkable.

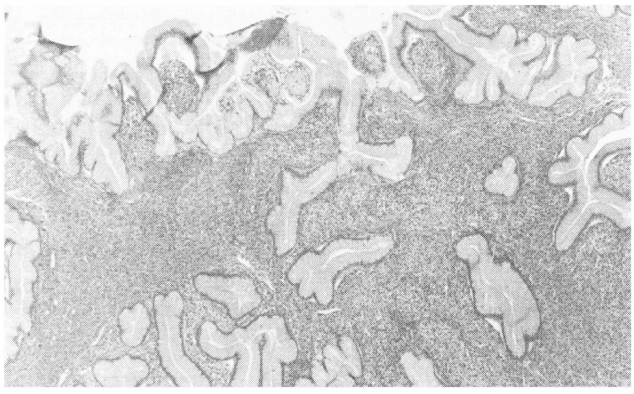
Immunohistochemical findings

The glandular mucinous epithelium showed focal positivity for human chorionic gonadotrophin (Figure 5). The cytoplasm of the luteinized stromal cells reacted strongly and diffusely with antiserum for vimentin (Figure 6). Also, the cytoplasm of the luteinized stromal cells showed focal intense positivity for synaptophysin (Figure 7), and focal mild positivity for human chorionic gonadotrophin (Figure 5). Staining results for oestrogen and progesterone receptors were negative.

Discussion

Ovarian mucinous cystadenomas are benign epithelial ovarian tumors that are usually characterized by multilocularity, smooth outer and inner surface, and contain mucinous fluid of variable consistency. These tumours tend to be large, unilateral cysts, sometimes reaching enormous proportions and yet still remain benign [11]. It is believed that mucinous cystadenoma usually arises from simple metaplasia of the germinal epithelium [12]. It may arise occasionally from a teratoma in which all the other elements have been blotted out and it rarely occurs from a Brenner tumour in which there has been mucinous transformation of the epithelium [12]. Ovarian mucinous tumours can show both exocrine and endocrine activity. Production of mucin is the result of their exocrine func-

Fig. 1



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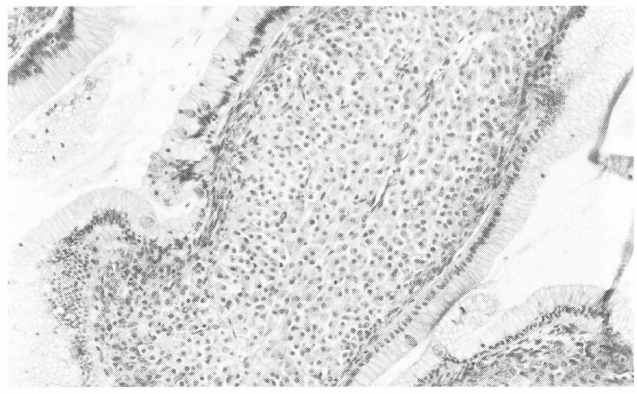

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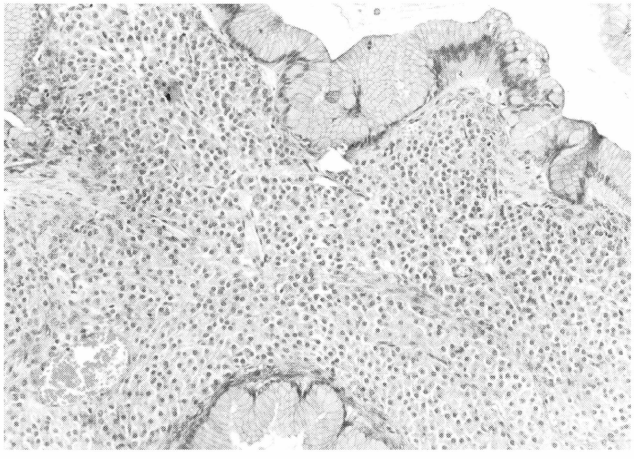

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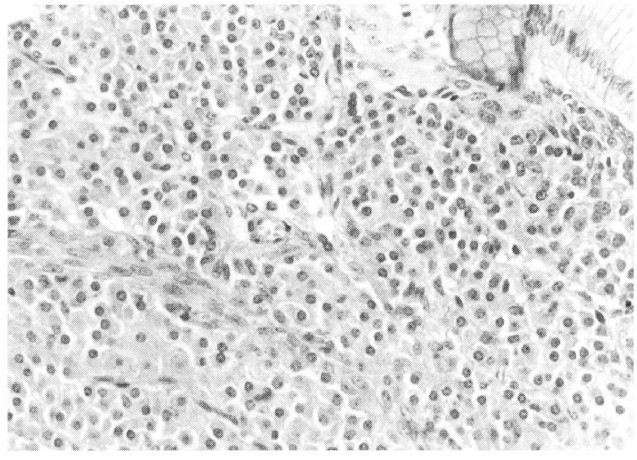

Figure 1. — Masses of luteinized cells are noted in the wall of the cyst below the mucinous epithelium (H&E x 40).
Figure 2. — The same as Figure 1 (H&E x 100).
Figure 3. — The same as Figure 1 (H&E x 200).
Figure 4. — The same as Figure 1 (H&E x 400).

tion, while oestrogenic or androgenic production is the result of their endocrine function [13].

In the majority of ovarian mucinous tumours (cystadenomas or cystadenocarcinomas) the hormone production is due to functioning ovarian stromal, which can be found even in postmenopausal patients [13, 14]. Detre and Földes described a case of mucinous cystadenocarcinoma in a 67-year old musculized patient [13]. Soon after the removal of the tumour the levels of serum testosterone decreased and the patient gradually lost the virile type of body hair [13]. Moreover, postmenopausal patients with mucinous ovarian tumours may exhibit symptoms attributable to elevated serum oestrogen levels [15]. MacDonald *et al.*, reported that increased amounts of androstenedione, which can be converted into oestrone, was produced by hyperplastic stromal cells of the ovary containing a mucinous cystadenocarcinoma [16]. Dennefors *et al.*, reported that stromal tissue dissected from ovarian stromal hyperplasia in postmenopausal women was found to secrete measurable amounts of androstenedione, oestradiol, and progesterone [17]. However, ovarian tumours with functioning stroma are more frequently found in mucinous tumours during pregnancy [6, 13, 18, 19]. The signs of muscularization of such patients usually regress or disappear after removal of the ovarian tumour or termination of pregnancy supporting the perception that the luteinized ovarian stromal cells are responsible for the androgen production. Indeed, in our patient the acne on the face and upper trunk cleared up one month after the operation. Hair growth on the chin, legs and abdomen returned to normal after two months and there was a marked reduction in the size of the clitoris. The patient experienced a normal menstrual period eight weeks postpartum. Serum androgen levels were normal on follow-up two months after surgery. In addition to that, the immunohistochemical study of our case showed focal positivity of the glandular epithelium and luteinized stromal cells for human chorionic gonadotropin supporting the hypothesis that intense human chorionic gonadotrophin stimulation during pregnancy may play a role in the metaplastic differentiation of mesenchymal cells of the ovarian stroma to androgen-producing lutein cells [6]. In our case the oestrogen and progesterone receptors were not expressed, although other studies have shown such expression [11]. It is of scientific interest that we have shown for the first time focal positivity of luteinized ovarian stromal cells for synaptophysin.

The luteinized stromal cells and the Leydig cells cannot be differentiated on morphological grounds [8]. It seems that original mesenchymal ovarian stromal cells are

Fig. 5

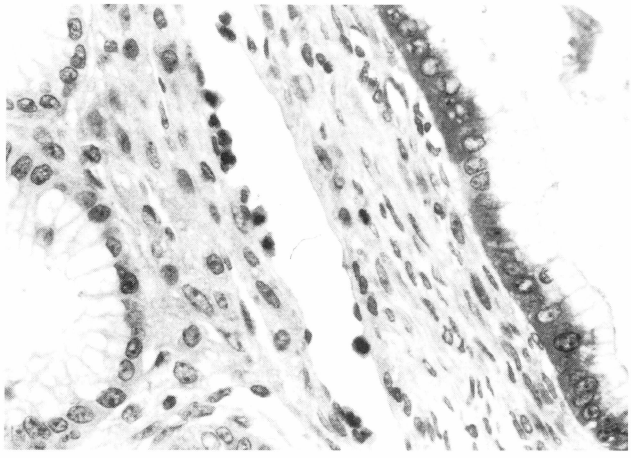

Fig. 6

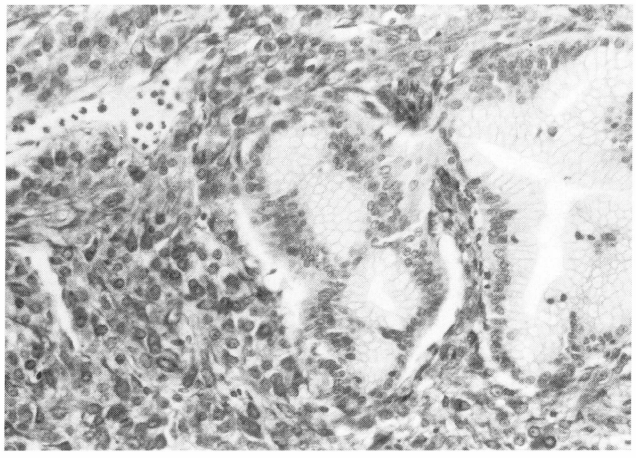

Fig. 7

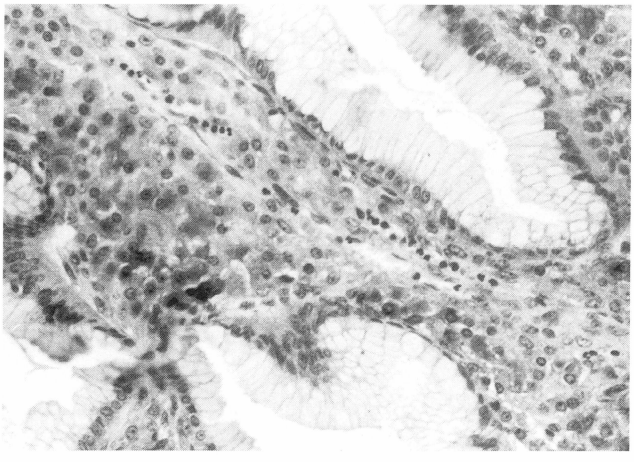

Figure 5. — Focal positivity of luteinized cells and glandular mucinous epithelium for human chorionic gonadotrophin (x 400).
Figure 6. — Strong and diffuse positivity for vimentin of the luteinized cells of the tumour (x 200).
Figure 7. — Focal positivity of luteinized cell for synaptophysin (x 200).

capable of profound differentiation into diffuse or cord-like tumours of the Leydig cell, luteinized thecal or stromal cells and granulosa-theca cell types. This stromal component has shown its ability to react as a totipotent ovarian mesenchyma with resultant hormone production and associated alterations in the host, i.e., feminization or muscularization [8, 20]. Therefore, a granulosa-theca cell tumour may give rise to virilization, whereas a Leydig cell tumour may result in feminization [8]. According to Novak and Woodruff, the production of virilizing as well as feminizing hormones could be explained by the original pluripotency of the ovarian mesenchymal cells [21]. In our case, histologically no crystalloids of Reinke were identified and the responsible cells for the virilization in our pregnant patient were thought to be lutein cells. When crystals of Reinke are identified in the lutein-like cells, these cells are interpreted as Leydig cells [4]. However, the detection of crystalloids of Reike is extremely difficult [22] and it has been shown that only 35% to 40% of all Leydig cell tumors of the testis contain crystalloids of Reinke detectable by light microscopy [22].

In conclusion, we have presented an unusual case of clinical virilization during pregnancy associated with an ovarian mucinous cystadenoma with functioning stroma. The virilizing manifestations disappeared after removal of the ovarian neoplasm, supporting the perception that the functioning ovarian stroma was responsible for the androgen production.

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